REMARKS

Claims 1, 2 and 5-20 are pending in the instant application. Claims 1, 2 and 5-20 have been rejected. Claims 12 and 17-20 have been canceled. Claims 1 and 16 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Restriction/Election

The Examiner has required restriction of the instant invention. As acknowledged by the Examiner, Applicants have amended claim 1 to refer to antisense compounds targeted to a single sequence, SEQ ID NO: 3.

II. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 1, 2 and 5-20 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that the term "specifically hybridizes with" is indefinite. In an earnest effort to advance the prosecution, Applicants have amended the

claims to make the language more clear. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 16-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense-mediated inhibition of p70 S6 kinase expression *in vitro* does not reasonably provide enablement for *in vivo* uses or methods of treating diseases; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* is highly unpredictable or problematic.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the

papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans.

The paper by Branch (1998) that is cited by the Examiner in support of her position teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. Nowhere does the reference of Branch teach that one of skill would be unable to use the compounds or methods of the invention in an *in vivo* environment.

The paper of Jen et al. (2000) is cited by the Examiner as discussing the challenges that remain in the use of antisense

before it becomes routine. However, again, this paper is not stating that results of well-designed *in vitro* studies would not provide one of skill in the art with assurance that *in vivo* activity is likely with a compound shown to have activity *in vitro*.

The paper by Green et al. (2000) is a review of the science of antisense and even discusses some of the clinical trials that are ongoing with antisense compounds. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Jen and Gewirtz (2000) also discusses the science of antisense technology and the fact that antisense is one of the tools currently being used to suppress gene expression. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

Further, the Examiner has failed to support the proposition that administration of antisense to p70 S6 kinase would be unpredictable based on any objective evidence. In contrast, data are provided in Example 15 showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro*. Therefore, Applicants have clearly met their burden under 112, first paragraph. Further, Applicants respectfully point out that the "absence of working examples should never be the sole

reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation". *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 16 and canceled claims 17-20. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 102

Claims 1, 2, 9-13, 15 and 16 have been rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Shimkets et al. (WO 01/47944). The Examiner suggests that this reference discloses oligonucleotides 50 nucleobases in length complementary to SEQ ID NO: 3 at residues 1610-1659 and residues 1655-1706, and antisense targeted to the complement of these sequences, as well as modifications as claimed. Applicants respectfully traverse this rejection.

At the outset, the claims have been amended to recite that the compounds of the instant invention are targeted to specific regions

within the sequence of p70 S6 kinase of SEQ ID NO: 3, regions other than the regions disclosed by Shimkets et al. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 92-96, Tables 1 and 2.

Shimkets et al. disclose oligonucleotides complementary to SEQ ID NO: 3 of the instant invention at two certain areas. Nowhere does this paper teach or suggest antisense targeted to specific regions of p70 S6 kinase of SEQ ID NO: 3 as now claimed. In order to anticipate a claim the reference cited must teach each and every limitation of the claim (MPEP 2131). Therefore, this reference cannot anticipate the claims as amended and withdrawal of this rejection is respectfully requested.

Claims 1, 2, 12, 13 and 15 have been rejected under 35 U.S.C. 102(e) as being anticipated by Plowman et al. (WO 01/77338). The Examiner suggests that this reference discloses a 25 mer oligonucleotide fully complementary to residues 1087-1111 of SEQ ID NO: 3. Applicants respectfully traverse this rejection.

As discussed *supra*, the claims have been amended to recite compounds targeted to specific regions within the sequence of p70 S6 kinase (SEQ ID NO: 3), regions that do not include the region disclosed by Plowman et al. Nowhere does this paper teach or suggest antisense targeted to specific regions of p70 S6 kinase of

SEQ ID NO: 3 as now claimed. In order to anticipate a claim the reference cited must teach each and every limitation of the claim (MPEP 2131). Therefore, this reference cannot anticipate the claims as amended and withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 12-16 have been rejected under 35 U.S.C. 102(a) as being anticipated by Yang et al. (2001). The Examiner suggests that this paper discloses a 21 mer antisense oligonucleotide targeted to a nucleic acid molecule encoding p70 S6 kinase and its use. Applicants respectfully traverse this rejection.

Yang et al. (2001) disclose a single antisense oligonucleotide targeted to p70 S6 kinase. However, this reference was published in August of 2001, and the filing date of the instant application was August 1, 2001. Therefore, this reference is not a valid prior art reference under 35 U.S.C. 102 and cannot anticipate the instant invention as it was published after the filing date of the instant invention. Therefore, withdrawal of this rejection is respectfully requested.

V. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 5-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Shimkets et al., in view of Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to incorporate the modifications taught by Baracchini et al. into the oligonucleotides taught by Shimkets et al. because such modifications were routine in the art. The Examiner suggests one of skill would have been motivated since the benefits of making modifications were well known in the art. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended the claims to recite that the antisense compounds of the instant invention are targeted to specific regions within the sequence of p70 S6 kinase (SEQ ID NO: 3). Also as discussed *supra*, the primary reference cited (Shimkets et al.) fails to disclose antisense compounds targeted to the specific regions as claimed. Accordingly the primary reference fails to teach or suggest the limitations of the claims as amended.

The secondary reference cited, even when combined with the primary reference, fails to overcome the deficiencies in teaching of this primary reference.

Baracchini et al. (US Patent 5,801,154) disclose the use of antisense compounds to modulate expression of multi-drug resistance-associated protein. However, nowhere does this paper teach or suggest that antisense compounds targeted to specific regions within the sequence of p70 S6 kinase (SEQ ID NO: 3)can be used to successfully inhibit gene expression in cells as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the art as combined fails to teach the limitations of the amended claims which recite antisense compounds targeted to specific regions within the sequence of p70 S6 kinase (SEQ ID NO: 3). Further, the combined art fails to provide one of skill with either the expectation of success or the motivation to combine the teachings. It is only with the specification in hand that one of skill would understand how to make and use compositions of the instant invention. MPEP 2143.01 states that the mere fact that references can be combined or modified is not sufficient to

establish *prima facie* obviousness. There must some suggestion or motivation in the reference to do so. Such suggestion or motivation is clearly lacking in the combination of references cited. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, 2 and 5-16 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (2001), in view of Baracchini et al. The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to make antisense as taught by Yang et al. and to incorporate modifications into the antisense as taught by Baracchini et al.. The Examiner suggests that motivation is provided by the combined teachings and what was known in the art. Applicants respectfully disagree with the Examiner's conclusions.

As discussed *supra*, the primary reference of Yang et al. is not a valid prior art reference as it was published after the filing date of the instant invention (August 1, 2001). Accordingly, this reference cannot be used to establish obviousness under 35 U.S.C. 103(a).

The secondary reference cited fails to teach the limitations of the claims by itself. To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First,

there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the art as combined fails to teach the limitations of the claims which recite antisense compounds targeted to p70 S6 kinase (SEQ ID NO: 3). Therefore, this combination of art cannot make obvious the instant invention, and withdrawal of this rejection is respectfully requested.

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: July 30, 2003
Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515